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Obesity at diagnosis and prostate cancer prognosis and recurrence risk following primary treatment by radical prostatectomy

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Abstract

Background: The association of obesity at diagnosis with prostate cancer progression is uncertain. This study aimed to examine the relationship between body mass index (BMI; 18.5-<25, 25-<30, 30-<35, ≥35kg/m^2) and prognostic risk at diagnosis, compare the concordance between prognostic risk assessed at diagnostic biopsy versus pathologic risk assessed at surgery across BMI categories, and investigate the association between obesity and prostate cancer recurrence and all-cause death.

Methods: We examined men enrolled in CaPSURE who underwent radical prostatectomy between 1995–2017. Multiple imputation methods were used to handle missing data and reported along with complete case findings.

Results: Participants (n=5,200) were followed for a median of 4.5 years; 685 experienced recurrence. Obesity was associated with higher prognostic risk at time of diagnosis (OR_{obese}=1.5; $OR_{very\ obese}$=1.7) and upward reclassification of disease between biopsy and surgery, driven by change in tumor stage (OR_{obese}=1.3; $OR_{very\ obese}$=1.6). We observed an association between BMI and recurrence with adjustment for disease severity using diagnostic factors ($HR_{very\ obese}$=1.7); this association disappeared when adjusting for disease severity factors obtained at surgery.

Conclusions: Our findings suggest that residual confounding may partially explain the conflicting evidence regarding obesity's influence on prostate cancer progression. Assessing T-stage via digital rectal exam may be complicated in larger men, potentially impacting clinical treatment decisions. A strong association with all-cause mortality demonstrates healthier BMI at diagnosis may still improve overall survival.

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Conflicts of Interest: The authors declare no potential conflicts of interest.

Impact: Patients with greater BMI are prone to more advanced disease at diagnosis and may be more likely to have their tumor stage underestimated at diagnosis.

Keywords

prostate cancer; obesity; diagnosis; cancer recurrence; screening

Introduction

Although prostate cancer is the 2nd-leading cause of cancer death among men in the United States, the severity of the disease varies considerably.[1–4] Much research has focused on identifying patient characteristics that predict prostate cancer mortality in an effort to target resources and avoid unnecessary interventions and the associated harms, while decreasing health care spending.[5] The relationship between obesity and prostate cancer outcomes is one area of active research and much debate. Biological responses to increased adiposity – such as changes in insulin-like growth factor, insulin, sex hormones, and adipokine signaling molecule concentrations – have been shown to promote prostate tumor growth in preclinical studies and have been associated with increased risk of prostate cancer progression and mortality in some, but not all, epidemiologic studies.[6–10] Specifically, while an increasing number of studies have found an association between obesity and increased risk of advanced prostate cancer and poorer outcomes following diagnosis, a few studies have found no evidence for these associations, leading to inconclusive evidence to recognize obesity as a formal risk factor for prostate cancer progression. For example, a literature review published in 2017 reviewed five recently published reports on the association between body mass index (BMI) and prostate cancer recurrence with different conclusions.[11] Two of these studies were conducted on the same sample of men, and the vastly different findings (HR point estimates 2.83 vs 0.83) were partially attributed to differences in covariate adjustments.[12,13] A 2013 meta-analysis noted similar contradicting evidence.[14]

In addition to a role in the biology of prostate cancer, adiposity may directly influence the efficacy of clinical screening and risk assessment using standard criteria applied to the population. Namely, the physical increases in blood volume and prostate gland size that occur with obesity may dilute prostate-specific antigen (PSA) levels and lessen the likelihood of finding small tumors on biopsy.[6,15,16] Additionally, careful digital rectal exam may be more difficult in obese patients. As a result, due to the mechanism by which information is obtained (i.e., via physical exam and needle biopsy in diagnostic setting versus via surgical removal and subsequent pathological evaluation of entire prostate gland), clinical assessment may underestimate true disease severity, particularly among obese versus normal weight men, leading to under treatment of obese men and an observed increase in risk of prostate cancer progression or death.[17–21]

The objectives of this study were to: (1) investigate the relationship between BMI and prognostic risk at diagnosis; (2) compare the concordance between prognostic risk factors (clinical Gleason score, stage) assessed at diagnostic biopsy versus pathologic risk at surgery (pathologic Gleason score, stage) across different BMI groups; and (3) investigate the association between obesity and outcomes (i.e., prostate cancer recurrence, all-cause

mortality) following radical prostatectomy adjusting for prognostic versus pathological risk. We hypothesized that obesity would be associated with higher prognostic risk at the time of diagnostic biopsy; obese men would have greater discordance between their prognostic risk assessed at the time of biopsy versus surgery (i.e., obese men would experience more misclassification of their disease severity at diagnosis compared to normal weight men and be more likely to experience an up-grade or up-stage from biopsy to surgery); and that obesity would be associated with increased risk of prostate cancer progression, independent of prognostic risk at diagnosis but not of pathological risk at surgery. To address these objectives, we utilized a unique data source, the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). With over 20 years of follow-up completed, CaPSURE offers a substantial number of participants and nearly 700 recurrence events, larger than most of the prior published studies on this topic.

Materials and Methods

Study Design

Data for this project were obtained from CaPSURE.[22,23] CaPSURE is a longitudinal observational registry that includes 15,310 men diagnosed with biopsy-proven prostate adenocarcinoma. Participants were recruited by participating urologists at 43 academic- and community- based urology practices across the United States, between 1995 and 2018. Data on clinical features including prognostic and pathologic factors (stage, Gleason score, PSA, etc.), treatments, and recurrences were reported by participating urologists. All participants provided written informed consent following institutional review board (IRB) approval. The study was conducted in accordance with the Belmont Report and U.S. Common Rule under local IRB supervision. Patients were followed until death or withdrawal from the study. Additional study details have been provided previously.[22,23]

Of the 15,310 CaPSURE participants, we excluded those without a primary treatment within nine months (n=1,128) and patients diagnosed prior to 1995 (n=2,369). We further excluded patients without radical prostatectomy as their primary treatment (n=6,590) and those diagnosed with metastasis (n=7). Due to the well-documented imbalance in both disease and mortality hazard of underweight individuals, participants with a BMI <18.5 kg/m^2 (underweight) were also excluded from this analysis (n=16) rather than being included in the normal weight category [24,25]. This left a total of 5,200 CaPSURE participants who met inclusion criteria (Figure 1); 3,230 (62%) of which had complete records. The remaining 1,970 (38%) had missing data on at least one variable of interest, with the majority of these missing BMI (n=1,353; see Missing Data section below).

Obesity Measures

Self-reported height and weight from the baseline questionnaire completed at diagnosis were used to calculate BMI. BMI was categorized as normal weight (18.5 to <25kg/m^2), overweight (25 to <30kg/m^2), obese (30 to < 35 kg/m^2), and very obese (≥35 kg/m^2).[26] We also examined obesity as a binary variable (≥30kg/m^2).

Outcome Measures

Disease severity at time of diagnosis was defined using a well-validated tool, the Cancer of the Prostate Risk Assessment (CAPRA), categorized as low (0–2), intermediate (3–5), or high score (≥6).[27–30] CAPRA uses age, stage, PSA, Gleason score, and percentage of positive biopsy cores to predict prognostic risk. Upward reclassification of disease risk was defined as an increase between the diagnostic and surgical values for either the Gleason score (change from <7 to ≥7) or T-stage (change from T1 or T2 to ≥T3) [Note: we use the term "T-stage" to refer to the T category of the TNM staging criteria]. Prostate cancer recurrence was defined as a PSA level ≥0.2ng/mL at two consecutive visits following radical prostatectomy, or a need for a secondary treatment at least 6 months after radical prostatectomy.[31–33] The date of recurrence was defined as the date of second PSA level ≥0.2ng/mL or the start date of second treatment. Time-to-event was thus measured from date of radical prostatectomy to date of recurrence. Patients without documentation of recurrence were censored at the date of last follow-up or death.

Mortality data was obtained from physician report, state death certificates, and queries to the National Death Index (NDI). Timing of the last NDI request allowed for follow-up through April 2017. The date of death was obtained from the death certificate and time-to-event was thus measured from date of radical prostatectomy to date of death. Patients without documented death were censored at the date of last follow-up.

Data Analysis

Multivariable ordinal logistic regression was used to investigate the association between BMI and disease severity at time of diagnosis, with the categorized CAPRA (i.e., disease severity) score as the outcome. A likelihood ratio test was used to test the proportional odds assumption. Multivariable logistic regression was used to investigate the association between BMI and upward reclassification of disease score and stage between diagnostic biopsy and surgical assessment. These models were both adjusted for age at diagnosis, race (white, black, other), smoking status (yes/no; reported at diagnosis), comorbidities (reported history (yes/no) of heart disease, hypertension, diabetes, and/or stroke), and type of CaPSURE site (academic, veteran, community-based). Odds ratios (OR) and associated 95% confidence intervals (CI) were reported.

Stratified Cox proportional hazards multivariable regression was used to investigate associations between BMI at date of diagnosis in relation to risk of prostate cancer recurrence and mortality. Models were stratified by CaPSURE site to account for the hierarchical structure of the data. Stratified Cox models allowed the unspecified baseline hazard to vary across the stratified variable (here, CaPSURE site), and are a common way to deal with clustering.[34] Hazard ratios (HR) and associated 95% CI were estimated relative to the normal weight group (BMI 18.5 to <25kg/m^2) or non-obese group (18.5 to <30kg/m^2). Covariates for multivariable analyses were determined *a priori* and included age at diagnosis, race, smoking status (reported at diagnosis), surgical approach (open, robotic, other), comorbidities, PSA (log-transformed continuous), and prognostic factors (Gleason score, T-stage, N-stage) obtained from diagnostic or surgical assessment.[32,35–37] Fine-Gray models were also fit to assess sensitivity to competing events when modeling recurrence.

Proportional hazards assumptions were investigated graphically using log-minus-log plots and statistically using Schoenfeld's test. Analysis was performed in Stata version 15.1 (College Station, Texas, USA).

Missing Data

BMI data were missing for 1,353 (26%) participants. Due to the high frequency of missing data on our primary predictor (BMI), we chose to use multiple imputation to handle missing data. Multiple imputation assumes data are missing at random. To assess the possibility that unobserved BMI data were missing *not* at random (which would suggest multiple imputation would not be appropriate), we pulled height and weight values from medical record data at one site on or near the date of diagnosis, for records with missing self-reported BMI (Figure 1). Using these data, we compared the distribution of the recovered (i.e., missing on self-report) BMI values to the distribution of reported BMI. Results suggested it was plausible data were missing at random (Supplemental Table S1).

Two methods for handling unobserved data were then used. First, we applied a complete case analysis, excluding from the analysis any individual with incomplete data.[38] Second, we performed multiple imputation via chained equations using the *chained* command in Stata, under the assumption that data are missing at random.[39] Multiple Imputation via Chained Equations is a multi-step process which first generates n (here, 50) complete plausible datasets using estimation (and re-estimation). Analyses are then run on each imputed dataset and results are pooled using Rubin's Rules.[40] Our imputation model included fully observed variables (age at diagnosis, race, surgical approach, death, time from surgery to recurrence, time from surgery to death, type of institution patient was treated at, and the CaPSURE site) and variables with incomplete values (BMI; patients' smoking, martial, and insurance status, education level, and income; PSA at diagnosis; total Gleason score, T-stage, and N-stage at biopsy and surgery; CAPRA; smoking status; presence of extracapsular extension, positive surgical margins, and seminal vesicle involvement at radical prostatectomy). The numbers of complete values and missing and imputed values for incomplete variables are shown in Supplemental Table S2.

Results

Of the 5,200 CaPSURE participants who met inclusion criteria, there were 3,230 complete cases; most incomplete records were considered incomplete due to missing BMI data (n = 1,353) and were subsequently excluded from complete case analyses. The remaining 617 records were missing data for at least one variable used in at least one model, and therefore, were only excluded from some of the complete case analyses.

Baseline patient and clinical characteristics are presented in Table 1 by BMI category. Overall, patients were followed for a median of 4.5 years (IQR: 2.1, 8.3) after radical prostatectomy. There were 685 patients with documented recurrence a median of 1.8 years (IQR: 1.0, 3.5) post-radical prostatectomy. Most patients recurred via elevated PSA value post-radical prostatectomy (n=510), rather than need for secondary treatment (n=175). A total of 671 deaths were observed during the follow-up period a median of 8.6 years (IQR: 5.1, 11.6) post-radical prostatectomy.

Clinical Presentation & Reclassification from Biopsy to Surgery

Adjusted imputation analysis of the association between BMI and clinical disease severity indicated that obese (OR_{obese} = 1.5, 95% CI: 1.2, 1.8) and very obese ($OR_{very\ obese}$ = 1.7, 95% CI: 1.2, 2.3) patients were more likely to have higher CAPRA scores at time of diagnosis, compared to their normal weight peers (Table 2). The association remained when we dichotomized obesity ($OR_{BMI\geq30}$ = 1.4; 95% CI: 1.2, 1.6). Results for the complete case analysis were similar (Table 2).

Overall, we detected a statistically significant association between BMI and upward reclassification among only the obese and very obese category of BMI in the imputed analysis ($OR_{overweight}$ = 1.1, 95%CI: 0.9, 1.3; OR_{obese} = 1.3, 95% CI 1.0, 1.6; $OR_{very\ obese}$ = 1.6, 95% CI: 1.1, 2.1). This association persisted when we dichotomized BMI ($OR_{BMI\geq30}$ = 1.3, 95% CI: 1.1, 1.5). There was a small positive, but not statistically significant association between obesity and upward reclassification of Gleason score (results shown in Table 3), suggesting the overall association was mainly driven by the upward reclassification of T-stage (results for T-stage reclassification: $OR_{overweight}$ = 1.2, 95%CI: 0.9, 1.5; OR_{obese} = 1.4, 95% CI 1.1, 1.8; $OR_{very\ obese}$ = 1.7, 95% CI: 1.1, 2.5). Results from the complete case analysis were similar (Table 3). Using the complete case data, we observed 550 subjects reclassified from a T1 or T2 to T-stage ≥ 3; 154 (28%) of these men were obese or very obese. More specifically, 14% of normal weight men were reclassified versus 16% of overweight, 19% of obese men, and 22% of very obese men ($p_{chi\text{-}sqaured}$=0.027). We further investigated the association between BMI at date of diagnosis and upward reclassification of disease using a mixed effects model to account for clustering at the site level (using clinical site in place of type of site) and the results were similar (data from mixed effects model not shown).

Recurrence and All Cause-Mortality

When we used the prognostic risk measures from diagnostic biopsy to adjust for disease severity to assess the association between BMI and various outcomes, we found some evidence that very obese (≥35 kg/m^2) patients were at greater risk of recurrence ($HR_{very\ obese}$ = 1.7, 95% CI: 1.1, 2.5; p-trend=0.066) and all-cause mortality ($HR_{very\ obese}$ = 1.7, 95% CI 1.1, 2.7; p-trend=0.001) in the imputed analysis (Table 4). Associations remained when we used the dichotomized version of BMI ($OR_{BMI\geq30;\ recurrence}$ = 1.2, 95% CI: 1.0, 1.5; $OR_{BMI\geq30;\ mortality}$ = 1.5, 95% CI: 1.2, 1.8). Similar results were observed in the complete case analysis (Table 4).

When we adjusted for disease severity based on pathologic risk factors from surgery (rather than prognostic risk from diagnostic biopsy), the associations between BMI and recurrence were positive but no longer statistically significant, even for the most obese patients ($HR_{very\ obese}$ = 1.3, 95% CI: 0.9, 2.0; p-trend=0.495). This was also observed using the dichotomized version of BMI ($HR_{BMI\geq30}$ = 1.2, 95%CI: 0.9, 1.4). The association between obesity and all-cause mortality remained after adjustment for prognostic risk factors at surgery using both the categorical ($HR_{very\ obese}$ = 1.7; 95% CI: 1.1, 2.6; p-trend=0.0012) and binary ($HR_{BMI\geq30}$ = 1.5; 95% CI: 1.2, 1.8) versions of BMI. In the complete case analysis, there was evidence of an overall association between BMI and all-cause mortality (p-

trend=0.008), though there was no statistically significant association observed within any single BMI category ($HR_{overweight}$ = 0.8, 95% CI: 0.6, 1.1; HR_{obese} = 1.2, 95% CI: 0.8, 1.6; $HR_{very\ obese}$ = 1.5, 95% CI: 0.9, 2.5); however, the binary version of BMI did capture this association ($HR_{BMI\geq 30}$ = 1.4, 95% CI: 1.1, 1.8). The rest of the findings were similar under the complete case analysis (Table 4).

We further considered adjustment for presence of positive surgical margins, but no meaningful change in the estimates were observed. We also further analyzed the association between BMI at date of diagnosis and prostate cancer recurrence while accommodating competing risks (i.e., death) by fitting Fine-Gray models, and the results did not materially differ from those reported from our simple stratified Cox model (data not shown).

Discussion

In this report, we attempted to elucidate the apparent discrepancies seen in the literature regarding the association between BMI and prostate cancer recurrence. Although counterexamples can be found, results from our models adjusting for measures of disease severity using prognostic risk factors from diagnostic biopsy are consistent with much of the literature that also used covariate data from the diagnostic biopsy, suggesting that BMI at diagnosis is independently associated with an increased risk of recurrence.[41–45] Next, when we instead used pathologic risk measures from surgery to adjust for disease severity, we observed no association, consistent with two reports in the literature that also adjusted for surgical measures.[46,47] A recent report contradicted this finding using a more stringent definition of recurrence (PSA >0.2 ng/mL on 2 consecutive visits).[48] Overall, these results support the conclusion that there may be residual confounding in studies examining BMI in relation to prostate cancer recurrence when analyses adjust for prognostic factors (e.g., stage and score) assessed via diagnostic biopsy versus using pathologic stage and score assessed from surgery. This may also explain apparent discrepancies in the literature.

Once surgical measurements were used to characterize disease severity, the independent associations of BMI with risk of recurrence was attenuated. This is not to say that obesity does not influence disease. In fact, we observed an increased CAPRA score (an indicator of disease severity) at time of diagnosis among more obese versus normal BMI men, consistent with more than a 2-fold increase in high prognostic risk disease for the very obese patients. This can have important implications for clinicians, suggesting patients with greater BMI are more likely to present with greater disease severity. Obese patients may present with worse prognostic risk disease due to later detection due to the physical presence of fat affecting sex hormones, adipokines signaling molecules, and insulin-like growth factor, which act to promote more aggressive disease.[6–9] This is also consistent with prior reports that have found that prostate volume, which increases with body size, can lead to difficulties in finding cancer.[49,50] Trends in Table 1 suggest increased presence of positive biopsy cores and slightly younger age may be partially driving increased CAPRA scores among the most obese men. Consequently, these results suggest that assessing tumor stage via digital rectal exam may be more difficult in larger men, which can impact clinical decisions regarding the type and urgency of subsequent treatment and highlights the need for additional research on the potential benefits of alternative screening or prognostication methods. Such tailored

approaches my help address the difficulties in detecting and staging disease in more obese patients (e.g., different PSA thresholds for different categories of BMI, or PSA with different imaging follow-up), as has been suggested by other authors.[15,50,51] Further, our findings indicate that obesity remains a predictor of all-cause mortality, regardless of whether we adjusted for prognostic factors at diagnostic biopsy or pathological measures obtained at surgery, consistent with our stated hypothesis. Given that most men with prostate cancer will die of a cause other than prostate cancer, these results underscore the importance of monitoring and reducing obesity among all men, including those with prostate cancer.

The analysis for the association between BMI and upward reclassification of disease showed an increased risk in reclassification for obese men. This association appears to be driven by a change in T-stage between diagnostic biopsy and pathology, determined after surgical removal of the prostate. These results are consistent with our hypothesis and suggest that assessing tumor stage via digital rectal exam may be more difficult – and in some cases, imaging may be less ideal – in larger men, which can impact clinical decisions regarding the type and urgency of subsequent treatment. Specifically, the reclassification of T-stage for 18% and 22% of reclassified obese and very obese men, respectively, resulted in a change in stage that likely would have impacted treatment decisions (i.e., T1 or T2 reclassified to T3 or T4), compared to only 14% of normal weight men.

In this study, we examined the extent and potential impact of the missing data on our reported estimates, with particular interest in the relatively large amount of missing BMI data. Results from our imputation analysis suggest that our estimates were not greatly affected by the missing data, to the extent that our missing at random assumption is true. Although we were unable to identify any systematic issues that resulted in a large number of missing BMI values, we were also unable to identify characteristic differences between those patients who reported BMI and those who did not (Supplemental Table S3). Further, where we were able to obtain data from patient charts to assess patterns of missingness, we gained confidence in the plausibility that our data were missing at random (Supplemental Table S1). Therefore, where our results differ, we put more stock in the results of the multiply imputed data, due to the potential bias that may arise in complete case analysis if data are not missing completely at random. In particular, results from our multiple imputation analysis were consistent with the complete case for all but one analysis, when examining the association between BMI and all-cause mortality. In that analysis, results from the imputation analysis were more consistent with the hypothesis that BMI increases the risk of all-cause death. However, because it is not possible to rule out that missing data are missing not-at-random, the slight difference in the complete case analysis and multiple imputation results should be interpreted cautiously.

Several limitations should be considered when interpreting these results. First, while there was a fair amount of missing data in BMI, great effort was made to assess the impact of this missing data and to use advanced analytical techniques to guide inferences. Second, as patients managed by modalities other than surgery do not have comprehensive pathologic review conducted on their tumors, this analysis was unable to incorporate patients who had undergone other forms of primary treatment, including radiation, watchful waiting, or active surveillance, although radical prostatectomy was the most common form of primary

treatment in CaPSURE. Given our findings, it may be of value for clinicians to take into account BMI when contemplating these other forms of treatment. Third, we recognize that BMI has been criticized for its inability to distinguish between different fat distributions within the body and may be less reflective of obesity in aging populations, however it is the most readily understood and widely used metric for measuring obesity. Fourth, we recognize that non-obese men may have different risk factors (other than BMI) for advanced grade and stage that increase their risk of recurrence, which could act to attenuate the association between obesity and prostate cancer recurrence. However, men in this study predominantly had localized disease, as they underwent radical prostatectomy as primary treatment. Therefore, this is unlikely to explain our null findings after adjustment for pathological factors obtained at surgery. Regardless, caution should be taken in generalizing our results to men diagnosed with advanced disease. Fifth, limited follow-up time and number of prostate cancer deaths precluded analysis of the association between BMI and prostate cancer specific mortality. Finally, due to the large concentration of white men in this study, care should be taken when generalizing these results to non-white populations.

Overall, we observed that patients with greater BMI are prone to more advanced disease at time of diagnosis and may be more likely to have their tumor stage underestimated at diagnostic biopsy. Further, results for BMI and the outcome of recurrence varied based on the type of measures used to adjust for disease severity (diagnostic biopsy vs. surgical pathology), which may help explain some of the discrepancy observed in the literature.These findings have important methodological implications, suggesting that surgical measures of disease severity may more accurately capture true disease status, particularly among obese men. Important clinical implications of these findings include the need for potentially different prognostic risk classifications and more accurate screening approaches for obese men, to best inform treatment decisions and aid earlier disease detection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body Mass Index
CAPRA	Cancer of the Prostate Risk Assessment score

CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
PSA	Prostate Specific Antigen

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Impact/ Significance:

Our findings suggest that patients with greater body mass index are prone to more advanced disease at time of diagnosis and may be more likely to have their tumor stage underestimated at diagnosis.

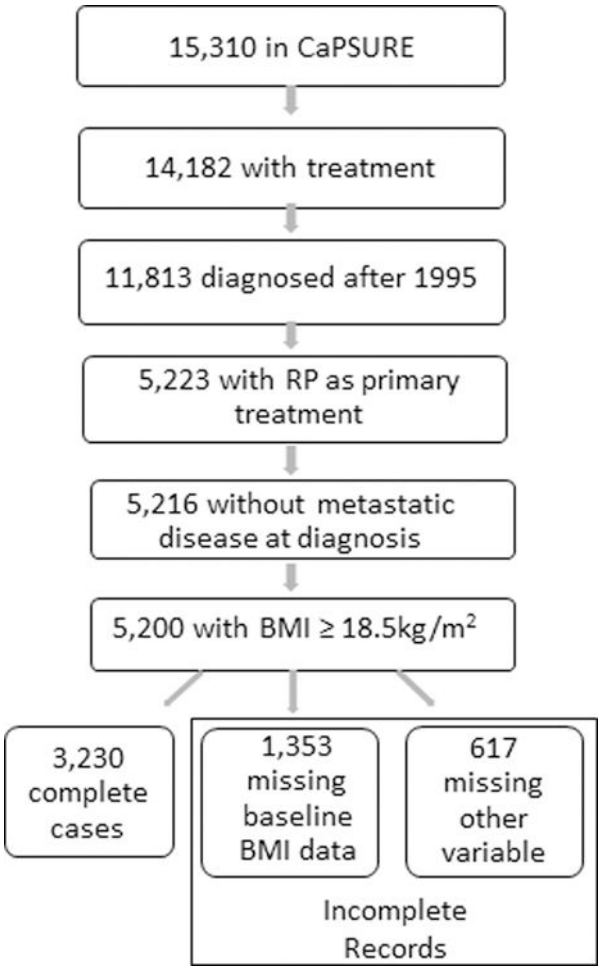

Fig. 1.

Patient flow chart showing inclusion of men with prostate cancer from CaPSURE cohort. Abbreviations: CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; RP – Radical Prostatectomy; BMI – body mass index.

Table 1.

Baseline patient and clinical characteristics of 5,200 CaPSURE patients who underwent radical prostatectomy

	BMI at diagnosis				
	Normal Weight (18.5 to <25 kg/m^2)	**Overweight (25 to <30 kg/m^2)**	**Obese (30 to <35 kg/m^2)**	**Very Obese (≥35 kg/m^2)**	**Missing**
	n (%) mean ± SD	**n (%) mean ± SD**	**n (%) mean ± SD**	**n (%) mean ± SD**	**n (%) mean ± SD**
N (%)	937 (18)	1,998 (38)	719 (14)	193 (4)	1353 (26)
Race					
White	861 (92)	1,809 (91)	635 (88)	169 (88)	1099 (81)
Black	52 (6)	134 (7)	59 (8)	18 (9)	186 (14)
Other	24 (3)	55 (3)	25 (3)	6 (3)	68 (5)
Age at diagnosis (yr)	61.8 ± 7.2	61.3 ± 6.8	61.1 ± 6.5	59.1 ± 6.3	60.1 ± 7.2
Current smoker	119 (13)	189 (9)	51 (7)	16 (8)	10 (1)
Surgical Approach					
Open	769 (82)	1,677 (84)	554 (77)	147 (76)	1,042 (77)
Robotic	124 (13)	232 (12)	118 (16)	28 (15)	249 (18)
Other	44 (5)	89 (4)	47 (7)	18 (9)	62 (5)
Comorbidity	355 (38)	1,024 (51)	460 (64)	144 (75)	37 (3)
Heart Disease	122 (13)	266 (13)	86 (12)	31 (16)	7 (1)
Hypertension	246 (26)	824 (41)	401 (56)	121 (63)	28 (2)
Diabetes	42 (4)	129 (7)	93 (13)	35 (18)	8 (1)
Stroke	45 (5)	85 (4)	30 (4)	8 (4)	2 (<1)
PSA (ng/dL) [a, b]	6.9 ± 4.8	6.9 ± 7.1	6.8 ± 47	6.2 ± 3.9	7.1 ± 5.2
≤ 6.0	523 (56)	1,178 (59)	399 (56)	116 (60)	705 (52)
> 6.0 to ≤ 10	262 (28)	515 (26)	185 (26)	51 (26)	398 (29)
> 10 to ≤ 20	101 (11)	193 (10)	82 (11)	14 (7)	164 (12)
> 20 to ≤ 30	19 (2)	30 (2)	9 (1)	3 (2)	26 (2)
> 30	7 (<1)	26 (1)	5 (<1)	0 (0)	10 (<1)
Total Gleason [a, b]	6.3 ± 0.8	6.3 ± 0.8	6.4 ± 0.8	6.4 ± 0.8	6.4 ± 0.8
<7	638 (68)	1,360 (68)	435 (61)	113 (59)	836 (62)
7	238 (25)	509 (25)	218 (30)	67 (35)	428 (32)
>7	51 (5)	95 (5)	56 (8)	11 (6)	79 (6)
T – Stage [a, b]					
T1	515 (55)	1,110 (56)	446 (62)	108 (56)	786 (58)
T2	378 (40)	795 (40)	237 (33)	72 (37)	477 (35)
T3	10 (1)	15 (1)	4 (<1)	2 (1)	14 (1)
T4	-	1 (<1)	-	-	-

	BMI at diagnosis				
	Normal Weight (18.5 to <25 kg/m^2)	Overweight (25 to <30 kg/m^2)	Obese (30 to <35 kg/m^2)	Very Obese (≥35 kg/m^2)	Missing
	n (%) mean ± SD	n (%) mean ± SD	n (%) mean ± SD	n (%) mean ± SD	n (%) mean ± SD
≥ 34% Positive Cores[a]	301 (32)	624 (31)	250 (35)	72 (37)	458 (34)
Positive Surgical Margins	214 (23)	466 (23)	197 (27)	60 (31)	350 (26)
Site Type					
Academic	116 (12)	195 (10)	68 (9)	27 (14)	110 (8)
Community	801 (85)	1,760 (88)	629 (87)	166 (86)	1,206 (89)
Veteran	20 (2)	43 (2)	22 (3)	-	37 (3)

[a] Obtained at diagnostic biopsy.

[b] n=179 with unknwon PSA; n=66 with unknown Gleason score; n=225 with unknown stage; n=242 with unknown % positive cores.

Abbreviations: yr = year; PSA = prostate specific antigen; T-stage = tumor stage

Table 2.

Results of ordinal logistic regression for the association between BMI and clinical disease severity (CAPRA) at time of diagnosis within imputed and complete case datasets

	Multiple Imputation Analysis		Complete Case Analysis	
	Crude OR (95%CI)	Adjusted[a] OR (95%CI)	Crude OR (95%CI)	Adjusted[a] OR (95%CI)
BMI Category				
Normal Weight	Ref	Ref	Ref	Ref
Over-Weight	1.09 (0.92, 1.29)	1.13 (0.95, 1.34)	1.05 (0.88, 1.25)	1.07 (0.89, 1.28)
Obese	1.37 (1.12, 1.68)	1.48 (1.20, 1.82)	1.39 (1.12, 1.72)	1.43 (1.14, 1.79)
Very Obese	1.47 (1.08, 1.99)	1.66 (1.21, 2.28)	1.54 (1.10, 2.15)	1.68 (1.19, 2.38)
Obese (kg/m^2)				
18.5 to <30	Ref	Ref	Ref	Ref
≥30	1.31 (1.13, 1.52)	1.39 (1.19, 1.62)	1.38 (1.17, 1.62)	1.41 (1.19, 1.67)

[a]ORs are estimated from ordinal logistic regression analysis for a one category increase in CAPRA score (categorized as 0–2, 3–5, or ≥6).

[b]Adjusted for age at diagnosis, race, smoking status, comorbidities, and site type. Abbreviations: OR – Odds ratio; CAPRA – Cancer of the Prostate Risk Assessment

Table 3.

Association of BMI and odds of upward reclassification of disease status between clinical and surgical assessment within imputed and complete case datasets

		Multiple Imputation Analysis		Complete Case Analysis	
	Reclassification events/total N[a]	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Crude OR (95% CI)	Adjusted[b] OR (95% CI)
Overall Upward Reclassification (Gleason score or T-stage)					
BMI Category					
Normal Weight	272/937	Ref	Ref	Ref	Ref
Over-Weight	603/1,998	1.06 (0.90, 1.24)	1.09 (0.92, 1.28)	1.06 (0.89, 1.25)	1.09 (0.91, 1.29)
Obese	245/719	1.22 (1.00, 1.49)	1.28 (1.04, 1.57)	1.26 (1.03, 1.56)	1.32 (1.07, 1.64)
Very Obese	77/193	1.47 (1.07, 2.01)	1.55 (1.12, 2.13)	1.62 (0.18, 2.24)	1.68 (1.21, 2.34)
p-trend		0.035	0.013	0.006	0.003
Obese (kg/m^2)					
18.5 to <30	875/2,935	Ref	Ref	Ref	Ref
≥30	322/912	1.22 (1.05, 1.42)	1.25 (1.07, 1.46)	1.28 (1.10, 1.50)	1.31 (1.12, 1.54)
Upward Reclassification of Gleason Score					
BMI Category					
Normal Weight	184/886	Ref	Ref	Ref	Ref
Over-Weight	400/1,888	1.01 (0.84, 1.22)	1.03 (0.85, 1.24)	1.03 (0.84, 1.25)	1.05 (0.86, 1.29)
Obese	160/683	1.12 (0.89, 1.39)	1.14 (0.91, 1.43)	1.17 (0.92, 1.48)	1.22 (0.95, 1.56)
Very Obese	48/185	1.28 (0.91, 1.80)	1.28 (0.90, 1.81)	1.34 (0.93, 1.93)	1.34 (0.92, 1.96)
p-trend		0.415	0.417	0.274	0.245
Obese (kg/m^2)					
18.5 to <30	584/2,774	Ref	Ref	Ref	Ref
≥30	208/868	1.14 (0.96, 1.34)	1.14 (0.96, 1.35)	1.19 (0.99, 1.42)	1.20 (0.99, 1.44)
Upward Reclassification of T-Stage					
BMI Category					
Normal Weight	118/818	Ref	Ref	Ref	Ref
Over-Weight	278/1,769	1.13 (0.91, 1.40)	1.16 (0.94, 1.45)	1.11 (0.88, 1.40)	1.12 (0.88, 1.42)
Obese	116/631	1.32 (1.02, 1.71)	1.39 (1.07, 1.80)	1.34 (1.01, 1.77)	1.37 (1.02, 1.82)
Very Obese	38/170	1.53 (1.04, 2.25)	1.66 (1.11, 2.46)	1.71 (1.13, 2.57)	1.81 (1.18, 2.75)
p-trend		0.063	0.022	0.029	0.018
Obese (kg/m^2)					
18.5 to <30	396/2,587	Ref	Ref	Ref	Ref
≥30	154/801	1.25 (1.04, 1.51)	1.29 (1.07, 1.56)	1.32 (1.07, 1.62)	1.34 (1.08, 1.65)

[a] Reclassificiation events and total N reported based on complete case dataset.

[b] Adjusted for age at diagnosis, race, smoking status, comorbidities, and site type. Abbreviations: OR – Odds ratio estimated from logistic regression analysis.

Table 4.

Association between BMI and prostate cancer outcome using clinical and surgical assessments within imputed and complete case datasets

	Multiple Imputation Analysis[a]			Complete Case Analysis[b]		
	Crude Analysis	Clinical Adjustment[c]	Surgical Adjustment[d]	Crude Analysis	Clinical Adjustment[c]	Surgical Adjustment[d]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Prostate Cancer Recurrence						
BMI						
Normal Weight	Ref	Ref	Ref	Ref	Ref	Ref
Over-Weight	1.07 (0.86, 1.32)	1.07 (0.86, 1.34)	1.04 (0.84, 1.29)	1.04 (0.84, 1.30)	1.04 (0.82, 1.30)	1.01 (0.81, 1.29)
Obese	1.19 (0.92, 1.54)	1.22 (0.93, 1.59)	1.15 (0.88, 1.50)	1.15 (0.88, 1.50)	1.16 (0.87, 1.54)	1.07 (0.80, 1.43)
Very Obese	1.51 (1.03, 2.20)	1.66 (1.10, 2.49)	1.32 (0.87, 2.00)	1.51 (1.03, 2.20)	1.68 (1.12, 2.53)	1.24 (0.78, 1.95)
p-trend	0.138	0.066	0.495	0.151	0.066	0.819
Obese (kg/m^2)						
18.5 to <30	Ref	Ref	Ref	Ref	Ref	Ref
≥30	1.20 (0.99, 1.45)	1.23 (1.01, 1.51)	1.15 (0.94, 1.41)	1.19 (0.98, 1.45)	1.23 (0.99, 1.52)	1.09 (0.87, 1.36)
All-Cause Mortality						
BMI						
Normal Weight	Ref	Ref	Ref	Ref	Ref	Ref
Over-Weight	0.78 (0.64, 0.95)	0.89 (0.72, 1.10)	0.90 (0.73, 1.12)	0.75 (0.61, 0.92)	0.79 (0.62, 1.00)	0.81 (0.62, 1.05)
Obese	1.01 (0.79, 1.30)	1.29 (0.98, 1.70)	1.30 (0.98, 1.72)	1.00 (0.77, 1.31)	1.26 (0.94, 1.69)	1.15 (0.83, 1.59)
Very Obese	1.08 (0.73, 1.61)	1.74 (1.12, 2.70)	1.70 (1.12, 2.60)	1.14 (0.75, 1.72)	1.76 (1.14, 2.72)	1.52 (0.93, 2.49)
p-trend	0.020	0.001	0.001	0.008	<0.001	0.008
Obese (kg/m^2)						
18.5 to <30	Ref	Ref	Ref	Ref	Ref	Ref
≥30	1.21 (1.00, 1.47)	1.47 (1.19, 1.82)	1.47 (1.18, 1.82)	1.25 (1.01, 1.54)	1.59 (1.27, 1.99)	1.41 (1.11, 1.80)

[a] Prostate cancer recurrence: n=685 events; median [IQR] time to event: 1.8 [1.0, 3.5]. All-cause mortality: n=671 events; median [IQR] time to event: 8.6 [5.1, 11.6].

[b] Prostate cancer recurrence: n=523 events; median [IQR] time to event: 1.8 [1.0, 3.6]. All-cause mortality: n=496 events; median [IQR] time to event: 8.8 [5.2, 11.8].

[c] Adjusted for age at diagnosis, race, smoking status, comorbidities, surgical approach, PSA, clinical Gleason score, clinical T-stage, clinical N-stage, and clinical site.

[d] Adjusted for age at diagnosis, race, smoking status, comorbidities, surgical approach, PSA, pathologic Gleason score, pathologic T-stage pathologic N-stage, and clinical site.

Abbreviations: HR – Hazards ratio estimated from Stratified Cox Proportional Hazards regression analysis, BMI – body mass index, IQR – interquartile range.